



Additional box B of RNA polymerase III promoter in SINE B1 can be functional

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ABSTRACT

Many genes of small RNAs and short interspersed elements (SINEs) are transcribed by RNA polymerase III due to an internal promoter that is composed of two boxes (A and B) spaced by 30–45 bp. Rodent SINE B1 originated from 7SL RNA, and a 29-bp tandem duplication took place in B1 at an early stage of its evolution. As a result of this duplication, an additional box B (named B') located at a distance of 79–82 bp from box A arose in SINE B1. Here we have shown that despite the unusually large distance between boxes A and B', they can form an active promoter. In chinchillas, guinea pigs, and other rodents belonging to clade Ctenochostrica, structure of the B' box was well preserved and closely resembles the canonical B box. One may suggest therefore, that box B' can functionally replace box B in those copies of B1 where the latter has lost activity due to mutations.

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1. Introduction

RNA polymerase III (pol III) transcribes genes of a number of small RNAs in eukaryotic cells. Such RNAs play an important role in transcription (7SK), splicing (U6), translation (tRNA, 5S rRNA) and its regulation (7SL PHK, BC1/BC200, VA-I/II, and EBER 1/2) (Dieci et al., 2007). Functions of many pol III-transcripts (for example, Y, Vault, 4.5SI, 4.5SH, and SnaR) remain unclear. Although transcription of some of those RNAs (U6, 7SK, Y) completely/directly depends on the promoter located in upstream sequences, most pol III-transcribed genes have an internal promoter located downstream from a transcription start site (Dieci et al., 2007). Except for 5S rRNA gene, such an internal promoter consists of two 11 bp boxes (A and B). The box A lies 8–15 bp downstream of a transcription start site and 30–45 bp upstream of the box B. Initiation of transcription at such a promoter (type 2 pol III promoter) begins with binding of transcriptional factor TFIIC with boxes A and B. TFIIC recruits another transcriptional factor, TFIIB, that can bind to an upstream DNA sequence (region – 20 to – 30). The complex recruits pol III that initiates transcription; the transcription terminates at a run of four or more T residues (Geiduschek and Tocchini-Valentini, 1988; Schramm and Hernandez, 2002).

Besides genes, pol III is able to transcribe SINEs (Kramerov and Vassetzky, 2005; Okada, 1991). Length of these mobile genetic elements varies from 100 to 500 bp. Eukaryotic genomes can contain multiple

(10^4 – 10^6) copies of a SINE species. Copies are not identical and their nucleotide sequences vary by up to 35%. Such sequences constitute a family, and a genome can harbor several SINE families. To date, about 120 SINE families have been described (Kramerov and Vassetzky, 2011). SINEs code no polypeptides, and they use reverse transcriptase encoded by long interspersed elements (LINEs) for their transposition (retrotransposition) (Dewannieux et al., 2003; Kajikawa and Okada, 2002). Most SINE families originated from tRNAs; however, some families were derived from 5S rRNA and 7SL RNA. The latter is 300 nt long, and together with six polypeptides, it forms a signal recognition particle (SRP) which targets specific proteins to the endoplasmic reticulum (Walter and Blobel, 1982). A 7SL RNA pseudogene with a deletion of 180 nt central region seems to have arisen in the common ancestor of Supraprimates mammals (Kriegs et al., 2007; Nishihara et al., 2002; Vassetzky et al., 2003). This event resulted in the appearance of SINE families B1 and Alu in rodent and primate genomes, respectively. In contrast to B1, Alu consists of two parts (left and right monomers), each of which demonstrates sequence similarity with 7SL RNA (Deininger et al., 1981).

Besides B1 element, there are copies of its evolutionary precursor, pB1, in rodent genomes (Quentin, 1994). The basic difference between pB1 and B1 is that the latter contains a 29-bp tandem duplication which, perhaps, has contributed to the success of B1 as a mobile element. Although this duplication was discovered a long time ago (Ullu and Tschudi, 1984), only recently have we noticed that it contained box B (Veniaminova et al., 2007). As a consequence, there is an additional sequence similar to box B in SINE B1. This sequence (box B') is located at 29 bp further downstream from the transcription start than the original box B. The question arises: can the box B' have promoter activity, despite an unusually large distance between it and box A. Here we have shown that the box B', together with the box A, can form an effective promoter for pol III. At the same time, we found that whereas the box B' is active in

Abbreviations: SINE, short interspersed element; LINE, long interspersed element; pol III, RNA polymerase III; PAAG, polyacrylamide gel; EAC, Ehrlich ascite carcinoma; AFP, α -fetoprotein; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; Rev-PL, pGEM-T plasmid polylinker region adjoined M13Rev sequences.

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Ctenohistrica rodents (clade II), it became inactive due to two single nucleotide substitutions in mouse-related species (clade III).

2. Materials and Methods

2.1. Plasmid constructs

B1 copy with 5'-flanking sequence (50 bp) from the first intron of mouse α -fetoprotein gene was obtained by PCR and cloned into pGEM-T vector. Constructs containing chinchilla B1 copies (Cla12, Cla13, Cla14) were obtained the same way using DNA of the previously described clones (Veniaminova et al., 2007) as templates. Transcription termination signal (T_S) was added to 3'-flanking sequences using PCR. PCR was also used for preparation of the constructs lacking genomic 5'-flanking sequences and short variants of B1. Mutations were introduced in boxes B and B' using "megaprimer" method (Sarkar and Sommer, 1990). Nucleotide sequences of primers used in the study are shown in Table S1.

2.2. Transcription *in vitro*

Transcription *in vitro* was performed as described by Weil et al. (1979), using whole Ehrlich ascite carcinoma (EAC) extract. Reaction mixture contained 0.5 μ g plasmid DNA, 14 μ l EAC cell extract and 12.5 μ Ci [α ³²P]GTP in final volume of 50 μ l of 10 mM HEPES, pH 7.9, 70 mM KCl, 2.5 mM MgCl₂, 0.5 mM DTT, 3 μ mol of ATP, CTP, and UTP, and 0.25 μ mol GTP. The mixture was incubated at 30 °C for 1 hour. After incubation, RNA from the reaction mixture was purified by phenol-chloroform extraction and precipitated with ethanol.

Transcription products were analyzed using electrophoresis in 6% PAAG containing tris-borate buffer, 8 M urea and 50% formamide. Using PAAG without formamide resulted in very pronounced smear of full-length B1 transcripts. (This phenomenon is probably due to the unusually strong secondary structure of the transcripts). The gel was dried, exposed against an X-ray film and quantified by Cyclone phosphorimager (Perkin-Elmer Life Sciences Inc., Boston, MA).

2.3. Search for B1 SINE copies in Guinea pig genome database

B1 SINE copies in the Guinea pig (*Cavia porcellus*) genome was searched using the BLAST-like alignment tool (BLAT) in the UCSC

genome browser (<http://genome.ucsc.edu/cgi-bin/hgBlat>). Multiple alignments were produced by the ClustalW program and manually adjusted in GeneDoc.

3. Results

3.1. Box B' of mouse B1 SINE is activated by two nucleotide substitutions

We began this study by investigating the effect of box B and B' sequences on the transcription of the well-studied B1 copy located in an intron of the mouse α -fetoprotein (AFP) gene (Goodier and Maraia, 1998). Like other murine B1s, this copy contains two single nucleotide substitutions in the box B' (G98C; C102A), which are common to B1 of all rodents from clade III. These substitutions can be expected to inactivate box B' (Fig. 1). In addition, there is a copy-specific substitution (T95C) in the box B' of that B1 copy.

This B1 SINE copy was designated AFP-B1 and cloned in pGEM-T vector with 63-bp genomic 5'-flanking sequence. Next, using site-directed mutagenesis, a construct BmutAFP-B1 containing trinucleotide CCT instead of TTC was obtained (Fig. 1). This substitution is expected to inactivate box B (Borodulina and Kramerov, 2008; Goodier and Maraia, 1998). Indeed, *in vitro* transcription of BmutAFP-B1 was only 5% of transcription level of the original AFP-B1 (Fig. 2). To confirm the box B inactivation we obtained AFP-B1 and BmutAFP-B1 short variants, which lacked the region containing box B'. No transcription of the short B1 variant with changed box B could be detected (Fig. 2).

Then the construct B'mutAFP-B1 containing three substitutions in the box B', that made its nucleotide sequence appropriate to canonic box B, was obtained (Fig. 1). This construct was transcribed *in vitro* twice as effective as the original AFP-B1 (Fig. 2). Another construct named BB'mutAFP-B1 contained the same changes in the box B' as well as the inactivated box B. *In vitro* transcription efficiencies of this construct and AFP-B1 were comparable (Fig. 2). Thus, if the box B is inactive, box B' is able to provide effective transcription *in vitro*, despite of the unusual large distance (82 bp) between the boxes A and B'.

3.2. Box B' of chinchilla B1 SINE can be functional

In our previous study, B1 SINEs from more than twenty rodent families were cloned and sequenced (Veniaminova et al., 2007). It was



Fig. 1. Nucleotide sequence of B1 SINE copy from an intron of the mouse alpha-fetoprotein gene (AFP-B1). The nucleotide substitutions were introduced in the original (nat, native) sequence to inactivate box B (Bmut) or activate box B' (B'mut). The substituted nucleotides and unchanged positions marked with dots. The 29-bp duplication that appeared in the B1 precursor is indicated by arrows under the alignment. The end of the short B1 variants obtained for nat and Bmut is marked by an asterisk. Sequences of the boxes A, B, and B' from the B1 SINE of the clade III consensus (Veniaminova et al., 2007) are given over alignment. Box B consensus sequence obtained in the analysis of tRNA genes is also present (R = A/G, W = A/T, Y = T/C, invariant nucleotides are underlined) (Rohan and Ketter, 1987). AFP-B1 tail ending with a transcription terminator (T_S) is in italic.

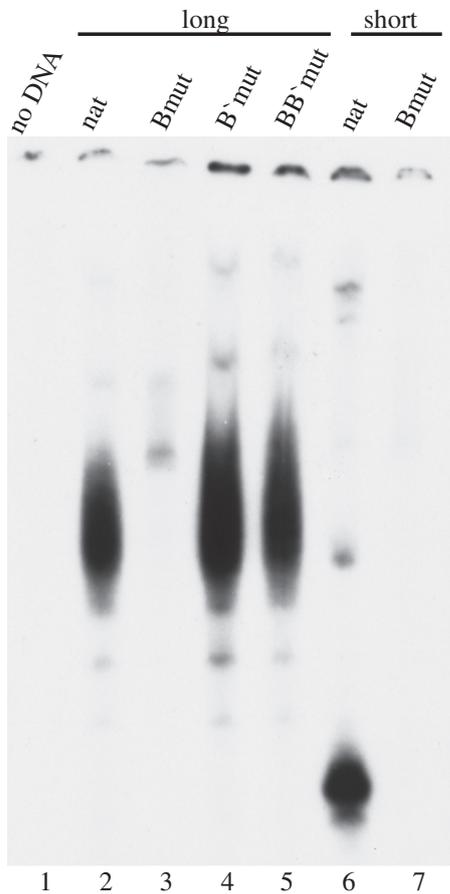


Fig. 2. *In vitro* transcription of constructs containing the original AFP-B1 SINE (nat) or AFP-B1 with changes in the boxes B and/or B'. See text and Fig. 1 for explanation of construct structures.

found that box B' in B1 consensus sequences of rodents from clade II (Ctenohipstrica) did not have nucleotide substitutions discussed above and typical for mice and related rodents (clade III). It could be expected that box B' of clade II rodents can function as a part of pol III promoter. To test this, three copies of B1 SINE cloned earlier from *Chinchilla laniger* genome were chosen for further study (Fig. 3). Clone Cla12 contained B1 with boxes A and B without mutations that could affect their function. In the clone Cla13 B1 element, there were several mutations in box B that were expected to completely inactivate it. Finally, there was only one nucleotide substitution in the Cla14 box B, which could decrease its promoter activity.

First, the experiment with constructs containing these B1 copies with their 52–97 bp genomic 5'-flanking sequence (designated as “nat”) was carried out. The most effective *in vitro* transcription was observed for construct natCla13; transcription of natCla12 was 12.5 fold lower, and no transcription of natCla14 was detected (Fig. 4).

Differences in the transcription efficiency observed in this experiment could be attributed to the influence of genomic 5'-flanking sequence. To normalize the 5'-flanking sequence influence, the B1 copies studied here were deprived of the adjacent genomic regions and inserted in pGEM-T vector in the same orientation. In such constructs, the beginning of B1 SINE were flanked by the pGEM-T polylinker (PL) fragment located near the standard M13Rev primer binding site. That 5'-flanking sequence was designated “Rev-PL” and the corresponding constructs - Rev-PL-Cla12, Rev-PL-Cla13, and Rev-PL-Cla14. (As we showed previously, 5'-flanking Rev-PL sequence had a positive effect on pol III *in vitro* transcription (Koval and Kramerov, 2009)).

Transcription of Cla13 and Cla14 B1 SINE copies dramatically changed after removal of their genomic 5'-flanking sequences (Fig. 4). The efficiency of Rev-PL-Cla13 transcription was only 19% of natCla13 transcription, whereas the efficiency of Rev-PL-Cla14 transcription greatly increased and became comparable with other studied B1 SINE copies. Efficiency of Rev-PL-Cla12 transcription increased approximately 2 fold. Thus, 5'-flanking sequences play a significant role in determining the effectiveness of transcription of the B1 SINE copies studied.



Fig. 3. Nucleotide sequence of three B1 SINE copies from the chinchilla genome. Upstream sequences are in lowercase letters and tail regions are in italic. Sequences of the boxes A, B, and B' from the B1 SINE of the clade II consensus (Veniaminova et al., 2007) are shown over the alignment. Box B consensus sequence obtained in the analysis of the tRNA genes is also present (R = A/G, W = A/T, Y = T/C, invariant nucleotides are underlined) (Rohan and Ketner, 1987). Nucleotides different from consensus of boxes B and B' are in bold. The end of the short variants of the studied B1 copies is marked by an asterisk. Cla12, Cla13, and Cla14 GenBank IDs: EF042431, EF042432, and EF042433, respectively (Veniaminova et al., 2007).

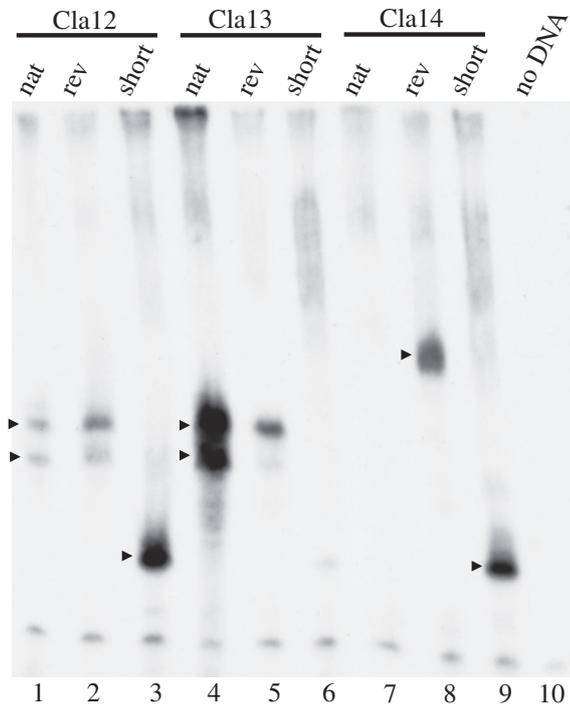


Fig. 4. *In vitro* transcription of constructs containing B1 SINE copies from the chinchilla genome. Genomic 5'upstream sequences were removed and saved in "rev" and "nat" constructs, respectively. "Short" constructs differ from "rev" constructs so that they contain 3'-truncated B1 element derivatives. Bands of interest are marked by arrowheads. See text and Fig. 3 for details.

It is important to note that all three copies of B1 in the constructs with the same 5'-flanking sequences (Rev-PL) were transcribed with comparable effectiveness although their intergenic promoter sequences differed. To determine a possible contribution of box B' to B1 SINE transcription the short variants of Cla12, Cla13 and Cla14 sequences (lacking the 3'-terminal region with the box B') were obtained. Boxes A and B which are necessary for pol III transcription were included in the remainder of the B1 SINE sequence.

In vitro transcription of shortCla14 and shortCla12 constructs was effective, whereas the level of shortCla13 transcription decreased 12-fold compared to a full-size variant (Rev-PL-Cla13) and was only 4% of the most actively transcribed shortCla12 (Fig. 4). Such low transcription of shortCla13 shows that box B in this B1 copy was damaged by mutations and became virtually inactive. On the other hand, the effective transcription of the full-size Cla13 sequence clearly demonstrated that box B' can functionally substitute box B during B1 SINE transcription. Thus, box B' is an integral part of pol III promoter in some copies of chinchilla B1 and, probably, other Ctenohystrica.

3.3. Boxes B and B' of B1 SINE copies in the Guinea pig genome

The Guinea pig (*Cavia porcellus*) genome has been sequenced recently. This allowed us to estimate the occurrence of B1 copies with damaged box B and functional box B' in the genome of a species of Ctenohystrica clade. Initially, we estimated the ratio of B1 among the 7SL RNA-derived SINEs of the guinea pig genome. On UCSC site all the 7SL RNA-derived SINEs in this genome were incorrectly annotated as pB1. All SINEs indicated as pB1 were extracted from a randomly chosen region (1.8 Mb) on scaffold 4. Among them, 131 copies contained 29-bp duplication and therefore were graded as B1 SINEs. The other 463 copies did not contain the duplication and were classified as pB1. Thus, B1 copies constitute approximately 22% of all 7SL RNA-derived SINEs in the guinea pig genome.

Then, 132 copies of B1 SINE (Suppl. Fig. 1) most similar to the previously deduced Ctenohystrica B1 consensus (Veniaminova et al., 2007) were extracted from the guinea pig genome database. It turned out that in 21.2% of B1 copies, both box B and box B' may be active, according to their nucleotide sequences. Both box B and B' were damaged in 25.7% of B1 copies and 17.4% of the copies contained the damaged box B'. Finally, in 35.6% of the B1 SINE copies, box B was damaged while box B' was potentially active. Thus, one might expect that about more than a third of all B1 SINE copies in the guinea pig genome can be transcribed due to box B', but not box B activity.

4. Discussion

Boxes A and B of an internal pol III promoter are spaced by 30–45 bp in multiple tRNA genes and tRNA-derived SINEs (Kramerov and Vassetzky, 2005; Okada and Ohshima, 1995). The distance between these boxes is unusually large (60 bp) in 7SL RNA and primate Alu element derived from this RNA. Due to deletions, this distance is less (50–53 bp) in another 7SL RNA-derived SINE, namely - in the B1 element of rodents (Quentin, 1994). An additional box B (box B') located at a distance of 79–82 bp from box A appeared in the B1 element as a result of a 29-bp tandem duplication (Veniaminova et al., 2007). Here we reported that box B' was able to promote pol III transcription, despite its extraordinary remoteness from box A. Previously, it was shown that increasing the distance between boxes A and B to 80 bp by introducing an insertion into VA1 and tRNA genes reduced efficiency of their pol III transcription 3- and 10-fold, respectively (Cannon et al., 1986; Ciliberto et al., 1982). The absence of such a dramatic decrease of transcription in our experiments with B1 element indicates that in a certain nucleotide context, the pol III promoter can be effective despite a rather great distance between its boxes. Since 7SL RNA gene has the longer distance between boxes A and B than VA1 and tRNA genes, one can speculate that 7SL-derived SINEs are more tolerant to increase of space between the boxes.

The 29-bp duplication which caused the formation of box B' occurred in a copy of the SINE pB1 in the common rodent ancestor of clades II and III (Veniaminova et al., 2007). The clade III, the greatest in the number of species (about 1500), is composed of 11 families; this clade includes various species of mice, rats, gerbils, hamsters, voles, mole rats, jerboas, and others. There are two nucleotide substitutions which inactivated box B' in these rodents. One might suggest that the box B' inactivation could promote proliferation of B1 in the genomes of the mouse-related rodents, e.g. by eliminating the possible conflict between boxes B and B'.

The clade II consists of 17 families and includes such rodents as guinea pigs, capybaras, chinchillas, nutrias, degus, porcupines, and many others. There are no common nucleotide substitutions inactivating box B' in those rodents, and when box B is mutated, box B' can functionally replace it, as we have shown here studying chinchilla B1s. For guinea pigs, the proportion of copies of B1 with damaged box B, and potentially active box B' was evaluated by us at 35.6%. Surprisingly, these B1 copies were found 2 times more frequently than the copies with a normal box B, but a defective box B'. The more frequent occurrence of B1 copies with active box B' compared with the copies that have a normal box B, but not box B', indicates that the former were even more successful SINEs than the latter.

It is difficult to judge what may underlie the different evolutionary ways of box B' in B1 elements of rodent clades II and III. A B1 master gene with mutations in the box B' could appear by chance just in early evolution of clade III. Thus, active and inactive boxes B' were fixed randomly in rodents of clades II and III, respectively. Alternatively, different ways of B1 evolution in these two rodent clades might have a reason. The confrontation of SINEs with cellular defense mechanisms which are intended to repress their transcription and retroposition seems to play an important role in SINE evolution. (Significant fluctuations in rate of SINE retroposition at different historical periods

illustrate this confrontation (Kass et al., 2000; Batzer and Deininger, 2002; Ohshima et al., 2003)). It is quite likely that the activity of box B' in clade II rodents and its inactivity in clade III rodents were fixed in response to possible differences between those defense mechanisms in rodents of the two clades.

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